Antibody Responses to \textit{Aspergillus fumigatus} Allergens in Patients with Cystic Fibrosis

L.K. Karla Arruda $^{a}$
A. Amy Muir $^{a}$
L.D. Lisa D. Vaiels $^{a}$
R.F. Robert F. Selden $^{b}$
T.A.E. Thomas A.E. Platts-Mills $^{a}$
M.D. Martin D. Chapman $^{a}$

Departments of $^{a}$Internal Medicine, and $^{b}$Pediatrics, Asthma and Allergic Diseases Center, University of Virginia Health Sciences Center, Charlottesville, Va., USA

Key Words
\textit{Aspergillus fumigatus}
Cystic fibrosis
Allergic bronchopulmonary aspergillosis
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Introduction
Fungi of the genus \textit{Aspergillus} are associated with a spectrum of human diseases including asthma, allergic bronchopulmonary aspergillosis (ABPA), aspergilloma and cystic fibrosis (CF). We have previously reported that CF patients have a significantly higher prevalence of IgE antibody (Ab) to \textit{Aspergillus fumigatus} (60%) than patients with asthma (6%). In addition, most CF patients (84%) had serum IgG Ab to \textit{A.fumigatus} allergen \textit{Asp f 1}. A subset of CF patients fulfilled the immunologic criteria for ABPA, including some children < 5 years old [1]. \textit{Asp f 1}, which is a major \textit{8-kO} \textit{A. fumigatus} allergen, is a member of the mito-gillin family of cytotoxins [2]. The complete nucleotide sequence of \textit{Asp f 1} has been determined [3], and recombinant \textit{Asp f 1} with IgE-binding activity has been produced [4]. In addition, \textit{Asp f 1} causes proliferative T cell responses in patients with ABPA [5]. Our studies suggested that CF patients are frequently colonized with \textit{A.fumigatus}, and that this colonization may contribute to the lung damage in some CF patients.

Methods and Results
We have extended the analysis of \textit{A. fumigatus} IgG and IgE Ab responses to a group of 119 CF patients (age 10 months^-6 years). IgG Ab was measured by antigen-binding RIA using 125I-labeled \textit{Asp f 1}, and IgE Ab to \textit{A. fumigatus} was quantitated by radioallergosorbent test. Eighty-nine percent of the patients had detectable IgG to \textit{Asp f 1}, and 14% fulfilled the immunologic criteria for ABPA. The RIA using 125I-labeled \textit{Asp f 1} was also used to monitor IgG Ab levels following antifungal therapy. Treatment of two CF patients with itraconazole over periods of 7 and 12 months resulted in a significant decrease in IgG Ab levels. In addition, a 6-year follow-up of a patient who presented with invasive aspergillosis and who was treated with surgery and amphotericin B [6] has shown a steady decrease (up to 65%) in the levels of IgG Ab to \textit{Asp f 1}. 

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To further identify A. fumigatus allergens, a cDNA library was prepared from A. fumigatus mycelial mRNA. IgE Ab of a serum pool obtained from 8 patients with CF or ABPA was used to screen the library. Three positive clones were isolated, containing inserts of 0.8-1.3 kb, and sequencing of the clones is in progress. Results of plaque immunoassays showed that 40-70% of CF patients had IgE Ab to these allergens.

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Discussion
Analysis of a large panel of serum from CF patients showed that a high percentage have IgG Ab to Asp f 1, a major A. fumigatus allergen. In keeping with previous studies, we found a prevalence of 14% of patients with immunologic criteria for ABPA. The results suggested that IgG Ab to Asp f 1 is a good marker for A. fumigatus colonization and can be used for evaluating antifungal treatment. Previous in vitro studies have shown that Asp f 1 is secreted into the culture medium upon germination of A. fumigatus spores, and that undetectable or very little Asp f 1 is present in spores or hyphae [3, 7]. It is possible that Asp f 1 may contribute to lung damage through IgE-mediated inflammation and/or direct cytotoxicity to lung tissue. Our results suggest that A. fumigatus in addition to Pseudomonas aeruginosa and Staphylococcus aureus should be considered as causes of lung disease in some patients with CF.

Although Asp f 1 appears to be a good marker for A. fumigatus colonization, there is evidence that Aspergillus spp. produce other allergens. Using IgE Ab from CF serum, we have isolated three cDNA clones from an A. fumigatus library. Identification and sequencing of A. fumigatus allergens other than Asp f 1 will allow further studies on the pathogenesis of Aspergillus-related diseases.

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References

